REMARKS

Currently, Claims 22-25, 28-29, 33-43, 46-48, 51, 59-62, 64, 66, 67, 69, 71-75, 80-106 and 108-116 are pending in the application. The changes made to the claims by the current amendment are attached hereto in a page entitled "Version with Markings to Show Changes Made." Claims 41-42, 73-74, 80-86, 90-91, 94-95, 97-100, and 102-104 were withdrawn from consideration.

In this communication, Applicant has amended Claims 22, 34, 39, 40, 43, 46, 48, 59, 62, 64, 66, 71, 72, 75, 87, 92, 93, 105, 106, 110, 111, 114, 115 and 116. Applicant has also cancelled Claims 78, 79, and 107 and added new claim 117. Applicant submits that the claim amendments do not introduce new subject matter and were made to more clearly define the claimed subject matter. Upon entry of the current amendment Claims 22-25, 28-29, 33-43, 46-48, 51, 59-62, 64, 66-67, 69, 71-75, 80-106, and 108-117 will be pending; a set of these claims is provided for the Examiner's convenience.

Attached hereto is a "VERSION WITH MARKINGS TO SHOW CHANGES MADE" to detail the amendments made to the claims.

35 USC §112 rejections

Claims 22-25, 28-29, 33-40, 43, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 78-79, 87-89, 92-93, 96, 101, and 105-106 were rejected under 35 USC §112(2) as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. In response, Applicant has amended the claims to more clearly define the subject matter. Claims 78 and 79 have been cancelled. To the extent it is maintained, Applicant traverses the rejection and requests reconsideration, arguing that the claim language is not indefinite.

The Office Action stated that Claim 22 remains incomplete for omitting essential steps as it is unclear how target cell/bead rosettes can be detected in the absence of a label, i.e. enzyme label for use in immunohistochemical staining.

Applicant responds that a step of coupling a label (e.g., an enzyme label) to the cell via the recited antibodies is not required for visualization of the target cell/bead rosettes. Target cell/bead rosettes are morphologically distinct from free cells and beads in a population of mixed cells using standard microscopy. See, for example, page 5, last

paragraph; page 6, first paragraph; page 8 second paragraph; and page 19-20, (Examples 3-7). The formation of the target cell/bead rosettes is sufficient for detection of the target cell among the mixed cells. Use of a label coupled to the antibodies is optional.

The Office Action also stated that Claim 22 lacks antecedent basis for, "the second antibody", "the cell mixture" and, "to bind the antibody". In response, Applicant has amended Claim 22 to provide sufficient antecedent basis for these terms.

The Office Action stated that Claim 46 is indefinite in reciting "capable of coating" because it fails to recite a positive limitation and that the specificities of the first and second antibodies do not appear to be consistent with their use as recited in Claim 22.

In response, Applicant has amended Claim 46 which now recites first and second antibodies, the function which is consistent with the use as recited in Claim 22. Applicant argues that the term "capable of coating" indeed recites a positive limitation as not all monoclonal antibodies can coat or bind paramagnetic particles without loss of the antigen binding ability of the antibody. Therefore Claim 46 recites use of antibodies having this feature.

The Office Action stated that Claim 48 remains incomplete for omitting essential steps as it is unclear how target cell/bead rosettes can be detected in the absence of a label, i.e. enzyme label for use in immunohistochemical staining. Applicant applies the same argument used in response to the rejection of Claim 22 to this rejection. The formation of the target cell/bead rosettes, without a label, is sufficient for detection of the target cell among the mixed cells.

The Office Action also stated that Claim 48 lacks antecedent basis for, "the second antibody", "the cell mixture" and, "to bind the antibody". In response, Applicant has amended Claim 48 in the same manner Claim 22 has been amended to provide sufficient antecedent basis for these terms.

The Office Action stated that Claim 62 is indefinite because the claim includes the word "low", which is a relative term. The Office Action also stated that the term "high" is not defined by the claim. In response, Applicant has amended Claim 62 removing the term "low"; however, the term "high" is not found in the Claim 62. If the rejection is maintained, Applicant respectfully requests clarification.

The Office Action stated that Claim 71 is indefinite because the claim includes the word "high", which is a relative term. In response, Applicant argues that in the context of this claim, "high" is not a relative term but rather is a part of the nomenclature of particular antigens recited in the claim. These antigen names have antecedent support in the specification in, for example, in Table 1 on pages 25 and 26. Applicant has not merely chosen use of "high" as a relative term but rather is using this term for identification of the antigen according the nomenclature established for the antigen in the prior art.

The Office Action stated that Claim 78 is indefinite for omitting essential structural cooperative relationships of elements and that the specificities of the claimed first and second antibodies in the kit are not consistent with the claimed method. In response, Applicant submits that Claim 78 has been cancelled.

The Office Action stated that Claim 87 remains incomplete for omitting essential steps as it is unclear how target cell/bead rosettes can be detected in the absence of a label, i.e. enzyme label for use in immunohistochemical staining. The Office Action also suggested the addition of "rosettes" after "tumor cell-bead". Applicant has amended Claim 87 to recite "rosettes" as suggested. In addition, Applicant applies the same argument used in response to the rejection of Claim 22 to this rejection of Claim 87 being incomplete. The formation of the target cell/bead rosettes, without a label, is sufficient for detection of the target cell among the mixed cells.

The Office Action stated that Claim 92 remains incomplete for omitting essential steps as it is unclear how target cell/bead rosettes can be detected in the absence of a label, i.e. enzyme label for use in immunohistochemical staining. Applicant applies the same argument used in response to the rejection of Claim 22 to this rejection. The formation of the target cell/bead rosettes, without a label, is sufficient for detection of the target cell among the mixed cells.

Therefore, Applicant submits that this rejection has been overcome by amendment, by the arguments presented herein, or by cancellation of claims. Applicant respectfully requests withdrawal of this rejection.

35 USC §112 rejections - New Matter

The Office Action has rejected Claims 110, 114, and 116 under 35 USC §112(1) as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the invention at the time the application was filed. The Office Action stated that the specification does not appear to provide any literal support for the recitation of "the target cells are detected at a sensitivity of one target cell per 100 or more total cells".

Applicant has amended Claims 110, 114, and 116, which now recite, "...wherein the target cells are detected at a sensitivity of one target cell per 1000 or more total cells". The specification provides support for this language on page 8, lines 16-24, and page 21, lines 13-15 (Example 8).

In light of the above amendment, Applicants submit that this rejection has been overcome and respectfully request its withdrawal.

35 USC §103 rejection

The Office Action has maintained the rejection of Claims 46-47, 78-79, 106, and 107 under 35 USC §103(a) over *Widder* et al. (EP 016,552; herein referred to as "*Widder*") and *Connelly* et al (U.S. Patent No. 5,422,277; herein referred to as "*Connelly*") in view of *Forrest* et al. (U.S. Patent No. 5,422,277, herein referred to as "*Forrest* "). In response Applicants have cancelled Claims 78, 79, and 107 and have amended claim 46.

To the extent that it is maintained, Applicants traverse this rejection arguing that a *prima facie* case of obviousness has not yet been established for this rejection under 35 USC § 103(a). Therefore, the burden of establishing a *prima facie* case of obviousness rejection remains with the Examiner. Applicants respectfully request reconsideration of this rejection.

Forrest teaches that avidin-biotin provides a very rapid and high binding affinity which offers the advantage of a more accurate and rapid assay.

To establish *prima facie* obviousness, three basic criteria must be met, namely: 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings; 2) a reasonable expectation of success; and 3) the references when combined must teach or suggest all the claim limitations. MPEP §2142.

Claim 46 recites a kit that has components suitable for performing the method of claim 22, the components including a first monoclonal antibody directed against a second antibody, a second monoclonal antibody directed against an antigen or receptor on a cell, and a paramagnetic bead. Claim 22 recites a method for detecting a specific target cell in a suspension of a mixed cell population. The first antibody is capable of being coated on the paramagnetic bead without losing its antigen-binding capability. The first antibody can also recognize the second antibody, which is directed to an antigen or receptor on the target cell.

Widder discloses a method for coarse separation of blood cells through use of microspheres having protein A associated with the outer surfaces thereof. However, *Widder* fails to teach a first antibody that binds a second antibody. *Connelly* does not overcome the deficiencies of *Widder*, as *Connelly* also fails to teach a first antibody that binds a second antibody, the second antibody, and a paramagnetic particle. Connelly directs the reader to a cell fixative composition for fixing the internal components of a cell without disrupting the cell surface components.

Indeed, the Office Action acknowledged that *Widder* and *Connelly* fail to teach that the first antibody is directed against a second antibody or antibody fragment that is directed against a cell membrane structure.

Forrest does not overcome the deficiencies of *Widder* and *Connelly*. *Forrest* teaches that avidin-biotin provides a very rapid and high binding affinity which offers the advantage of a more accurate and rapid assay. There is no teaching or suggestion of the first antibody that binds a second antibody, second antibody, and a paramagnetic particle required by the instant claims. A combination of *Widder, Connelly* and *Forrest* would, at best, achieve magnetic beads coated with protein A, an antibody, fixative reagents and an avidin-biotin labeling system. Such a combination would not achieve the instant invention. Additionally, there is no motivation for combining the teachings to make the combination.

Therefore, *Widder*, *Connelly*, and *Forrest*, taken alone or in combination, do not teach all the elements of the claimed invention. Therefore, all of the criteria for establishing a *prima facie* case of obviousness rejection has not been met.

Applicants respectfully request this rejection be withdrawn.

The Office Action has rejected Claims 22-25, 28-29, 33, 37-38, 51, 59-62, 64, 69, 101, 105, and 108-111 under 35 USC §103(a) over *Widder* et al. (EP 016,552) in view of *Connelly* et al. (U.S. Patent No. 5,422,277) in further view of *Abram* et al. (U.S. Patent No. 4,422,277, herein referred to as "*Abram*"). Applicants traverse this rejection arguing that a *prima facie* case of obviousness has not yet been established for this rejection under 35 USC § 103(a). Therefore, the burden of establishing a *prima facie* case of obviousness rejection remains with the Examiner. Applicants respectfully request reconsideration of this rejection.

The requirement for establishing a *prima facie* case of obviousness rejection have been detailed above. Applicants submit that the requirements for a *prima facie* case of obviousness rejection have not been met since the references do not teach all the elements of the claimed invention.

The teachings of *Widder* and *Connelly* have been discussed previously. Applicant has argued that *Widder* and *Connelly* are deficient in the teaching the detection of a specific target cell in a cell suspension using paramagnetic particles or beads coated with a monoclonal antibody or antibody fragment directed against a membrane structure specifically expressed on the target-cell and not on a non-target-cell in the cell suspension, forming target cell-bead rosettes, and quantitating the target cell-bead rosettes. In addition, the Office Action has acknowledged that 1) *Widder* and *Connelly* fail to teach that the first antibody is directed against a second antibody or antibody fragment that is directed against a cell membrane structure and that 2) *Widder* fails to teach the use of antibody to immobilize antibodies on the surface of the magnetic particles and that incubation of the antibody coated microspheres in mild detergent for 5-10 minutes to 2 hours at 4C.

Abram does not cure the deficiencies of *Widder* and *Connelly* and is further removed from the concept of the claimed invention. Abram teaches the detection of a

Neisseria gonorrhoeae antigen using a solid phase immunoassay. As detailed in Example 1, antigen released from lysed bacteria containing *N gonorrhoeae* are immobilized on a plastic bead. An anti-gonococcal antibody is then used to probe the antigen on the bead followed by incubation of the probed beads with an HRP-labeled secondary antibody against the anti-gonococcal antibody followed by colorometric quantitation of the amount of antigen via spectrophotometry.

Abram does not teach a first antibody that is directed against second antibody or antibody fragment that is directed against a cell membrane structure. Instead of detecting a membrane structure on an intact target cell, the antibodies described by *Abram* are directed to antigens from lysed bacteria that have been absorbed onto plastic beads. Furthermore *Abram* is deficient in teaching the coating of magnetic particles with a first antibody or antibody fragment directed against a second antibody. *Abram* is also deficient in describing the steps of d) mixing the coated paramagnetic particles with the washed cell mixture, e) incubating the washed cell mixture and the coated paramagnetic particles under gentle rotation at about 4°C until target cell-bead rosettes are formed, and f) visually detecting the target cell-bead rosettes after incubation.

Therefore, *Widder*, *Connelly*, and *Abram*, taken alone or in combination, do not teach all the elements of the claimed invention. Therefore, all of the criteria for establishing a *prima facie* case of obviousness rejection have not been met.

Applicants respectfully request this rejection be withdrawn.

The Office Action has rejected Claims 22, 46-48, 78-79, 106, 107 and 112-115 under 35 USC §103(a) over *Widder* et al. (EP 016,552) and *Connelly* et al. (U.S. Patent No. 5,422,277) in view of *Forrest* et al. (U.S. Patent No. 4,659,678) and in further view of *Abram* et al. (U.S. Patent No. 4,422,277). Applicant respectfully traverses the rejection.

The Office Action has rejected Claims 22, 34-36, 39, 40, 43, 48, 66, 67, 71, 72, 75, 87-89, 92, 93, 96 and 116 under 35 USC §103(a) over *Widder* et al. (EP 016,552) and *Connelly* et al. (U.S. Patent No. 5,422,277) in view of *Kemmer* et al. and *Holmes* et al., and in further view of *Abram* et al. (U.S. Patent No. 4,422,277). Applicant respectfully traverses the rejection.

The teachings of the references have been discussed previously. The Examiner acknowledges that none of *Widder*, *Connelly*, *Forrest, Kemmer* or *Holmes* teach a first antibody directed against a second antibody or antibody fragment that is directed against a cell membrane structure. Regarding *Abram,* instead of detecting a membrane structure on an intact target cell, the antibodies described by *Abram* are directed to antigens from lysed bacteria that have been absorbed onto plastic beads. *Abram* is deficient in teaching the coating of magnetic particles with a first antibody or antibody fragment directed against a second antibody. *Abram* is also deficient in describing the steps of d) mixing the coated paramagnetic particles with the washed cell mixture, e) incubating the washed cell mixture and the coated paramagnetic particles under gentle rotation at about 4°C until target cell-bead rosettes are formed, and f) visually detecting the target cell-bead rosettes after incubation.

In response to Applicant's previous arguments, the Examiner states that the features upon which applicant relies (i.e. paramagnetic particles are coated with antibodies which are directed against primary antibodies that recognize cell membrane structures in target cells wherein the primary antibodies are first incubated with the cell suspension containing the target cells and washed prior to contacting with the coated paramagnetic particles) are not recited in the rejected claims. These features are all clearly recited in the independent claims. Claim 22 clearly recites paramagnetic particles coated with antibodies directed against a second antibody (see step a). The second antibody recognizes cell membrane structures in target cells (see step b). The second antibody is incubated with the cell suspension prior to contact with the particles (see step b). The cell suspension-particle mixture is washed prior to contact with the particles (see steps c and d).

Applicants submit that since the claims clearly recite the features the Examiner has inferred have not been rejected, all claims are distinguished over the prior art.

In view of the remarks presented herein, Applicants respectfully submit that the claims are in condition for allowance. Notification to that effect is earnestly solicited. If prosecution of this case could be facilitated by a telephonic interview, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

22. (Three Times Amended) A method for detecting a specific target cell in a cell suspension of a mixed cell population, in a fluid system containing a mixed cell population, or in a cell suspension prepared from a solid tissue, with the exception of normal and malignant hematopoietic cells in blood and bone marrow, the method comprising the steps of:

a. coating paramagnetic particles or beads with a first antibody or antibody fragment directed against [the] a second antibody or antibody fragment;

b. incubating the second antibody or antibody fragment with the cell [mixture] suspension to bind the second antibody or antibody fragment with the target cell, thereby creating a cell mixture, wherein the second antibody or antibody fragment is directed against a membrane structure specifically expressed on the target cell and not on a non-target cell in the cell mixture;

c. washing the cell mixture to remove unbound second antibody or antibody fragment;

d. mixing the coated paramagnetic particles or beads with the washed cell mixture;

e. incubating the washed cell mixture and the coated paramagnetic particles under gentle rotation at about 4°C until target cell-bead rosettes are formed; and

f. visually detecting the target cell-bead rosettes after incubation.

34. (Amended) The method of claim 22, wherein the [monoclonal] second antibody or fragment thereof is directed against an antigen or a receptor in a cell with abnormal developmental patterns.

39. (Amended) The method of claim 22, wherein the [monoclonal] second antibody or antibody fragment is directed against fibronectin receptor, β-integrin, vitronectin receptor, αγß3-integrin, P-seletin including GMP-140, CD44-variants, N-CAM including

CD-56, E-cadherin, Le^y, carcinoembryonic antigen or CEA, EGF receptor, c-erbB-2 including HER2, transferin receptor, TNF-receptor, molecular weight antigen, p95-100, sarcoma antigens including TP-1 and TP-3 epitope, Mv 200kD, Mv160kD, MOC-31 epitope including cluster 2 epithelial antigen, MUC-1 antigen including DF3-epitope and gp290kD, prostate molecular antigen, TAG 72, bladder carcinoma antigen, Mv 48kD colorectal carcinoma antigen, lung carcinoma antigen Mv 350-420kD, Mel-14 epitope, $ß_2$-microglobulin, Apo-1 epitope, or pan-human cell antigen.

40. (Amended) The method of claim 22, wherein the [monoclonal] second antibody or antibody fragment is directed against a growth factor receptor or an oncogene product expressed on the membrane of a malignant cell.

43. (Amended) The method of claim 34, wherein the [monoclonal] second antibody or antibody fragment is directed against breast, ovarian or lung carcinoma cells; melanoma, sarcoma, glioblastoma or cancer cells of the gastrointestinal tract; melanoma, sarcoma, glioblastoma or cancer cells of the genitourinary tract; or melanoma, sarcoma, glioblastoma or cancer cells of the reticuloendothelial system.

46. (Three Times Amended) A kit for performing the method of claim 22, the kit comprising:

a. a first antibody, wherein said first antibody is a specific monoclonal antibody or antibody fragment directed against a second antibody or antibody fragment, [to an antigen on a target-cell, which monoclonal antibody or fragment is] said first antibody capable of coating a paramagnetic particle or bead without removing its antigen-binding ability;

b. a paramagnetic particle or bead; and

c. a second antibody, wherein said second antibody is a specific monoclonal antibody or antibody fragment directed against an antigen or a receptor within or on the target cell;

wherein said second antibody or antibody fragment is conjugated to a detectable label.

48. (Four Times Amended) A method for detecting a specific target cell in a cell suspension of a mixed cell population, in a fluid system containing a mixed cell population, or in a cell suspension prepared from a solid tissue, with the exception of normal and malignant hematopoietic cells in blood and bone marrow, the method comprising the steps of:

a. coating paramagnetic particles or beads with a first antibody directed against a second antibody or antibody fragment;

b. incubating the second antibody or antibody fragment with the cell [mixture] suspension to bind the second antibody or antibody fragment with the target cell, thereby creating a cell mixture, wherein the second antibody or antibody fragment is directed against a membrane structure specifically expressed on the target cell and not on a non-target cell in the cell mixture;

c. washing the cell mixture to remove unbound second antibody or antibody fragment;

d. mixing the coated paramagnetic particles with the washed cell mixture;

e. incubating the washed cell mixture and coated paramagnetic particles under gentle rotation at about 4°C until target cell-bead rosettes are formed; and

f. visually detecting the target cell-bead rosettes.

59. (Amended) The method of claim 48, wherein the second [monoclonal] antibody or antibody fragment directed against a membrane structure specifically expressed on the target-cell is a murine or a human antibody or fragment thereof.

62. (Three Times Amended) The method of claim 48, wherein [when the density of target-cells is low, or] when the ratio of target cell/total cells in the cell mixture is $\leq 1\%$, the method further comprises after incubating, applying a magnetic field to separate out the target cell-bead rosettes.

64. (Amended) The method of claim 48, wherein [quantitating]visually detecting includes counting the target cell-bead rosettes using a microscope or a cell or particle counting device.

66. (Amended) The method of claim 48, wherein the second [monoclonal] antibody or fragment thereof is directed against an antigen or a receptor in a cell with abnormal developmental patterns.

71. (Amended) The method of claim 48, wherein the second antibody or antibody fragment is directed against fibronectin receptor, β-integrin, vitronectin receptor, αγß3-integrin, P-selectin, GMP-140, CD44-variants, N-CAM, E-cadherin, Le^y, CEA, EGF receptor, c-erbB-2, HER2, transferin receptor, TNF-receptor, high molecular weight antigen, p95-100, TP-1 and TP-3 epitope, Mv 200kD, Mv160kD, MOC-31 epitope, cluster 2 epithelial antigen, MUC-1 antigen, DF3-epitope, gp290kD, prostate high molecular antigen, TAG 72, bladder carcinoma antigen, Mv 48kD colorectal carcinoma antigen, lung carcinoma antigen Mv 350-420kD, Mel-14 epitope, $ß_2$-microglobulin, Apo-1 epitope, or pan-human cell antigen.

72. (Amended) The method of claim 48, wherein the second [monoclonal] antibody or antibody fragment is directed against a growth factor receptor or an oncogene product expressed on the membrane of a malignant cell.

75. (Amended) The method of claim 66, wherein the second [monoclonal] antibody or antibody fragment is directed against breast, ovarian or lung carcinoma cells; melanoma, sarcoma, glioblastoma or cancer cells of the gastrointestinal tract; melanoma, sarcoma, glioblastoma or cancer cells of the genitourinary tract; or melanoma, sarcoma, glioblastoma or cancer cells of the reticuloendothelial system.

87. (Two Times Amended) A method for detecting tumor cells in a cell suspension of mixed cell population or in a cell suspension prepared from a solid tissue, with the

exception of normal and malignant hematopoietic cells in blood and bone marrow, comprising:

a) coating paramagnetic particles with a first antibody or fragment directed against a second [a] tumor-specific monoclonal antibody or fragment;

b) incubating the second tumor specific antibody with the cell suspension to allow the second tumor specific antibody to bind the tumor cells;

c) washing the cell suspension to remove unbound second antibody or antibody fragment;

d) mixing the coated paramagnetic particles with the cell suspension;

e) incubating the mixture at about 4°C under gentle rotation until tumor cell-bead rosettes are formed; and

f) visually detecting the tumor cell-bead rosettes.

92. (Amended) A method of detecting metastatic cancer cells in a suspension of a mixed cell population or in a single cell suspension from a solid tissue when the metastatic cancer cells are present at less than 1% of the cell suspension, the method comprising the steps of:

a) coating paramagnetic particles with a first antibody or fragment thereof directed against a second [a] cancer-specific monoclonal antibody or fragment;

b) incubating the second [tumor] cancer-specific antibody with the cell suspension to allow the second [tumor] cancer-specific antibody to bind the [tumor]cancer cells;

c) washing the cell suspension to remove unbound second antibody or antibody fragment;

d) mixing the coated paramagnetic particles or beads with the cell suspension;

e) incubating the mixture under gentle rotation at about 4°C until [tumor]cancer cell-bead rosettes are formed;

f) applying a magnetic field to separate out the [tumor]cancer cell-bead rosettes; and

g) visually detecting the [tumor]cancer cell-bead rosettes.

93. (Amended) A method according to claim [87]92, wherein the [tumor]cancer-specific monoclonal antibody is specific for [tumor]cancer antigens comprising a growth factor receptor, an oncogene product expressed on the membrane of a malignant cell, an adhesion membrane molecule, an MDR protein, breast, ovarian or lung carcinoma cells; melanoma, sarcoma, glioblastoma or cancer cells of the gastrointestinal tract; melanoma, sarcoma, glioblastoma or cancer cells of the genitourinary tract; or melanoma, sarcoma, glioblastoma or cancer cells of the reticuloendothelial system.

105. (Amended) The method of claim [33]22, wherein [quantitating]visually detecting includes counting the target bead rosettes using a microscope or a cell or particle counting device.

106. (Amended) The kit of claim 46, comprising a paramagnetic particle or bead coated with the first antibody and a paramagnetic particle or bead not coated with antibody.

110. (Once Amended) The method according to claim 22, wherein the target cells are detected at a sensitivity of one target cell per [100]1000 or more total cells.

111. (Amended) The method according to claim 22, wherein the second antibody is an IgG antibody [ant]and the first antibody recognizes the Fc-portion of the second antibody.

114. (Once Amended) The method according to claim 48, wherein the target cells are detected at a sensitivity of one target cell per [100]1000 or more total cells.

115. (Amended) The method according to claim 48, wherein the second antibody is an IgG antibody [ant]and the first antibody recognizes the Fc-portion of the second antibody.

116. (Once Amended) The method according to claim 87, wherein the target cells are detected at a sensitivity of one target cell per [100]1000 or more total cells.

117. (New) A kit for performing the method of claim 22, the kit comprising:

a. a first antibody, wherein said first antibody is a specific monoclonal antibody or antibody fragment directed against a second antibody or antibody fragment, said first antibody capable of coating a paramagnetic particle or bead without removing its antigen-binding ability;

b. a paramagnetic particle or bead; and

c. a second antibody, wherein said second antibody is a specific monoclonal antibody or antibody fragment directed against an antigen or a receptor within or on the target cell, wherein the second antibody or antibody fragment is directed against fibronectin receptor, β-integrin, vitronectin receptor, αγß3-integrin, P-seletin including GMP-140, CD44-variants, N-CAM including CD-56, E-cadherin, Le^{Y}, carcinoembryonic antigen or CEA, EGF receptor, c-erbB-2 including HER2, transferin receptor, TNF-receptor, molecular weight antigen, p95-100, sarcoma antigens including TP-1 and TP-3 epitope, Mv 200kD, Mv160kD, MOC-31 epitope including cluster 2 epithelial antigen, MUC-1 antigen including DF3-epitope and gp290kD, prostate molecular antigen, TAG 72, bladder carcinoma antigen, Mv 48kD colorectal carcinoma antigen, lung carcinoma antigen Mv 350-420kD, Mel-14 epitope, $ß_2$-microglobulin, Apo-1 epitope, or pan-human cell antigen;

wherein said second antibody or antibody fragment is conjugated to a detectable label.

Claims 78, 79, and 107 have been cancelled.